REMARKS

In the Office Action dated March 19, 2003, Claims 2-6, 8-17, 25-26, 32, and 38-40 are pending and currently under consideration. The Examiner requires that Applicant delete all mention of figures as they had allegedly never been submitted and if now submitted would be new matter. The Examiner has retained the rejection of Claims 6 and 12-14 under 35 U.S.C. § 112, first paragraph, as allegedly lacking descriptive support. The Examiner has also retained the rejection of Claims 2, 4-5, 8, 10-11, 25-26, 32 and 39-40 under 35 U.S.C. § 112, first paragraph, as allegedly lacking descriptive support. The specification has been objected to because on page 5, line 12 the specification refers to SEQ ID NO: 2 as human SAG DNA. Claims 2-6, 8-17, 25-26, 32, 38-40 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support. Claims 25-26 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 2 and 9 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Boehringer Manheim Biochemicals Catalog 1994.

This response addresses each of the Examiner's objections and rejections. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

The Examiner requires Applicant to delete all mention of figures since they had allegedly never been submitted and if now submitted would be new matter. In response, Applicant respectfully directs the Examiner's attention to the copy of a facsimile, attached herewith as Exhibit A, which states that all drawings were submitted upon the request of the Examiner after having previously been submitted at the filing date. Accordingly, the requirement to delete all figures is obviated and withdrawal thereof is respectfully requested.

Claims 6 and 12-14 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking descriptive support. Specifically, the Examiner indicates that the submitted ATCC receipt is insufficient to meet all the criteria set forth in MPEP 608/01(p)(C)[1] and no declaration that meets those criteria has been submitted. The Examiner states that in addition to the conditions under the Budapest Treaty, Applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

In response, Applicant respectfully submits that all restrictions on availability of the deposited host cells to the public will be irrevocably removed upon the granting of the patent based upon the present application and the host cells will remain permanently available for a term of at least 5 years after the most recent request for the furnishing of a sample, and in any case, for a period of at least 30 years after the date of deposit or for the enforceable life of the U.S. patent whichever is longer. In the event that the host cells become non-viable or are inadvertently destroyed, such will be replaced with viable host cells of the same taxonomic description.

Accordingly, the rejection of Claims 6 and 12-14 under 35 U.S.C. § 112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 2, 4-5, 8, 10-11, 25-26, 32 and 39-40 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking descriptive support. Specifically, the Examiner alleges that Claims 2, 4-5, 8, 10-11, 25-26, 32 and 39-40, as written, still read on nucleic acid sequences which minimally contain portions of SEQ ID NO: 1 or 3 and the claims are still drawn to a large genus of molecules. With respect to Claims 39 and 40, the Examiner indicates that the specification discloses that a motif search using the GCG program did not reveal any known

[1] Applicant believes that the Examiner intended to cite MPEP 608.01(p).

functional domains, although the Examiner acknowledges each of the putative proteins does contain two heme binding sites and one zinc finger domain. The Examiner thus concludes that no structures have been identified that are specifically directed to either an apoptosis protective function or a lipid peroxidation protective function. The Examiner further alleges that the specification fails to provide sufficient descriptive information, such as definitive structural features of the claimed genus of polynucleotides. The Examiner alleges that there is no description of the conserved regions which are critical to the structure and function of the genus claimed.

Applicant observes that the specification discloses novel isolated and purified DNA molecules of sensitive to apoptosis genes (SAG), e.g., mouse SAG (SEQ ID NO: 1) and human SAG (SEQ ID NO: 3), and DNA molecules substantially similar to SEQ ID NO: 1 or SEQ ID NO: 3. See e.g., page 5, lines 9-15. The specification also discloses that SAG proteins contain conserved heme binding sites and zinc finger domain. See, e.g., page 15, line 28 to page 16, line10. The specification further provides examples that demonstrate the function of the zinc finger domain and heme binding site in SAG protein. Specifically, the specification discloses that the zinc finger domain in the SAG protein protects cells against apoptosis. See, e.g., page 29, lines 24-30. The specification also discloses that the heme binding site in the SAG protein acts as an oxygen radical scavenger to prevent oxygen radical induced damage. See, e.g., page 32, line 24 to page 33, line 3.

Accordingly, Applicant submits that Claims 2, 4-5, 8, 10-11, 25-26, 32 and 39-40 are fully supported by the written description of the specification. However, in an effort to expedite favorable prosecution, Applicant has amended Claims 2, 8 and 39-40 and added Claim 42. Support for the amendment can be found throughout the specification, e.g., on page 16, lines

16-18 (for Claims 2, 8 and 42), in Example 16 starting at page 29 (for Claim 39) and in Example 19 starting at page 32 (for Claim 40). Claims 2, 4-5, 8, 10-11, 25-26, 32 and Claims 39-40 in the current form recite structures that are specifically directed to either an apoptosis protective function or a lipid peroxidation protective function.

With respect to the motif search using the GCG program as disclosed in Example 2, Applicant respectfully submits that the examples provided in the present application are intended for purpose of illustration and should not be construed to limit the scope of the invention. Applicant further submits that, at most, the fact that the GCG program did not reveal any known functional domain merely indicates that according to the GCG data base at the time the search was conducted, the art had not linked the function and the structures of SAG as disclosed and taught in the present invention. Thus, the motif analysis presented in Example 2 does not undermine the specific teaching of the present application that the apoptosis protective function and the lipid peroxidation protective function are linked to the structures of the zinc finger domain and heme binding site(s) respectively on SAG.

Applicant respectfully submits that the analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. *MPEP* § 2163. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. In view of the disclosures in the present application and the amended Claims 2, 8 and 39-40, Applicant submits that the present application has provided sufficient descriptive support that

one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Therefore, the rejection of Claims 2, 4-5, 8, 10-11, 25-26, 32 and 39-40 under 35 U.S.C. § 112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

The specification has been objected to because on page 5, line 12 the specification refers to SEQ ID NO: 2 as human SAG DNA. The Examiner indicates that the Paper Copy of the sequence listing reveals that SEQ ID NO: 2 is a 113 amino acid sequence. The Examiner requires that Applicant make appropriate corrections.

In response, Applicant respectfully submits that the recitation on page 5, line 12 of the specification referring to SEQ ID NO: 2 as human SAG DNA is an inadvertent typographical error. Applicant has amended the specification to correct the error. Support for the amendment can be found throughout the specification, on page 2, lines 26-27, for example. No new matter is added. Accordingly, the specification on page 5, line 12, as amended, refers to SEQ ID NO: 3 as human SAG DNA. Therefore, the objection to the specification is obviated and withdrawal thereof is respectfully requested.

Claims 2-6, 8-17, 25-26, 32, 38-40 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support. Specifically, the Examiner alleges that the uses of the claimed nucleic acid molecules or the encoded proteins, i.e., cancer treatment, diagnosis of cancer and protection against lipid oxidation, are not enabled. The Examiner cites numerous references. For example, the Examiner states that researchers have "many concerns" towards antisense technology (Gura, *Science*, 1995, 270:575-77)("Gura"). The Examiner further alleges that the status of the field of gene therapy <u>in humans</u> was unpredictable at the time the present invention was made. By citing Orkin et al. (Report and Rcommendations of the Panel to Access the NIH investment in Research on Gene Therapy, 1995) ("Orkin et al."), the Examiner alleges

that clinical efficacy of gene therapy has not been definitively demonstrated. The Examiner also alleges that the vector system used in animal models for delivering genes lacks efficiency for human gene therapy. Thus, the Examiner concludes that it cannot be predicted from the disclosure how to use the claimed DNA molecule for cancer treatment.

With respect to the diagnosis of cancer by detecting deletion mutants of SAG polypeptide, the Examiner alleges that based on the cell culture data presented in the present invention, in the absence of data provided from primary tumor cells and normal controls, no one of skilled in the art would believe it more likely than not that the present invention would be used as contemplated or as claimed in Claims 25 and 26. With respect to the protein encoded by the claimed nucleic acid molecule, the Examiner states that the asserted uses for the protein are for protection against lipid oxidation, for protection against apoptosis. The Examiner acknowledges that the specification provides a cell free assay to support the use for protection against lipid oxidation. However, the Examiner alleges that the exemplified assay is not commensurate in scope with the asserted use of the claimed invention. The Examiner also alleges that the specification provides no working examples as to how to use the claimed invention for protection against oxidation. With respect to protection against apoptosis, the Examiner alleges that the specification provides no guidance or examples regarding use of the claimed process. With respect to the use as an oxygen radical scavenger, the Examiner indicates that Example 19 states that the oxidative buffering activity of the SAG protein may qualify SAG as an oxygen radical scavenger (emphasis added by the Examiner). Thus, the Examiner alleges that Applicant cannot predict whether or not the encoded protein will function as claimed.

In the first instance, Applicant respectfully directs the Examiner's attention to fact that Claims 2-6, 8-17, 25-26, 32, 38-40 are not directed to the treatment for cancer, *per se*.

However, Applicant submits that the present application fully enables newly added Claim 41 directed to the inhibition of tumor growth by expressing an antisense strand of the claimed DNA molecules in tumor cells. Support for Claim 41 can be found throughout the specification, in Examples 17-18 starting on page 30 and original Claim 31, for example.

Applicant also notes that the Examiner cites numerous references, most of which were published in 1994-1995. Applicant respectfully directs the Examiner's attention to the fact that the present invention was filed in March 2000. The relevant technology, e.g., gene therapy, had significantly advanced from 1995 to 2000.

Applicant observes that Gura merely reports that certain side effects occurred when administering synthetic antisense oligonucleotides. Applicant also obseraves that while acknowledging that clinical efficacy of gene therapy has not been definitively demonstrated, Orkin et al. state that "the expectation and the promise of gene therapy are great." With respect to the diagnosis of cancer, Applicant observes that the specification discloses that cancer can be diagnosed using SAG as a marker (see, e.g., Example 21, on page 33). Applicant observes that in Example 21, the specification discloses that samples of both cancer and normal tissues from 12 patients were analyzed using routine technologies. The result of Example 21 revealed that SAG mutations are cancer-specific, i.e., not in normal tissues.

Applicant respectfully submits that the present invention is directed to a novel gene and polypeptide derived therefrom encoding a redox-sensitive protein that protects cell from apoptosis and promotes cell growth. Therefore the novel gene and the polypeptide of the present invention are useful for detection of genetic mutations of the gene, protection against apoptosis and scavenging of oxygen radicals; the expression of the antisense strand of the novel gene is useful for inhibition of tumor cell growth and therapeutic applications by gene therapy.

Applicant submits that the specification provides a sufficient teaching, using techniques well established and available to those skilled in the art regarding the identification and cloning of the SAG gene in both mouse and human (e.g., in Examples 1 and 2, on pages 13-16), expression and purification of the SAG proteins (e.g., in Example 6, on pages 18-20) and how to make single and double SAG mutants in heme binding sites and the zinc finger motif (e.g., in Example 8, on pages 21-23). The present application also provides specific teachings that SAG expression protects cells from DNA fragmentation, a hallmark of apoptosis (e.g., in Example 16, on pages 29-30); that antisense SAG expression inhibits tumor cell growth (e.g., in Example 17, on pages 30-31); that SAG can be used as a target in cancer gene therapy by expressing antisense SAG (e.g., in Example 18, pages 31-32); that SAG functions as an oxygen radical scavenger (e.g., in Example 19, on pages 32-33); that SAG mutations are cancer specific and can be used for diagnosing cancer (e.g., in Example 21, on pages 33-34); that SAG acts as a protector against lipid peroxidation (e.g., in Example 25, on pages 37-38); and that SAG protects against neuronal apoptosis (e.g., in Example 27, on pages 39-40). Therefore, the specification has provided sufficient description, guidance and working examples for those skilled in the art to make and use the claimed invention. Applicants respectfully submit that, as a matter of law, there is no requirement under 35 U.S.C. § 112, first paragraph, for the present application necessarily to include human or clinical trial data. The alleged unpredictability illustrated by the references cited by the Examiner, e.g., clinical efficacy in human gene therapy is, at best, general and cannot negate the specific, successful invention embodied in the present claims. Therefore, the cited references are irrelevant as to the enablement of the claimed invention. Applicant further submits that although the specification does not provide a working example, 35 U.S.C. § 112 does not require an applicant to provide a working example for making and using the invention if

the description of the invention itself is sufficient to permit one skilled in the art to make and use the invention, as is the case here.

Applicant acknowledges that additional experimentation, e.g., adjustment of certain parameters in different patients, may be required. However, such experimentation is routine to one skilled in the art and is not undue. Necessary experimentation is not determinative of the question of enablement; only *undue* experimentation is fatal under the provisions of 35 U.S.C. §112, first paragraph. *See, In re Wands*, 858 F.2d. 731, 736-737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

In addition, Applicant has amended the paragraph in Example 19, starting on page 32, line 24, to recite that the "oxidative buffering activity can qualify SAG as an oxygen radical scavenger" (emphasis added). As such, Applicant submits that the present invention teaches that the SAG proteins will function as claimed.

Accordingly, Applicant submits that the present application provides sufficient information for one skilled in the art to make and use the present invention, in the absence of undue experimentation. Therefore, the rejection of Claims 2-6, 8-17, 25-26, 32, 38-40, under 35 U.S.C. § 112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 15-17, 25-26, 32 and 38 have been further rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support. Specifically, the Examiner alleges that the specification, while enabling for SEQ ID NOs 1 and 3 as well as the claimed vectors and host cells, does not provide enablement for mutants of SEQ ID NOs 1 and 3. The Examiner acknowledges that the specification teaches two deletion mutations of SAG (SAG mutant-1 as set forth in SEQ ID NO: 11 and SAG mutant-2 as set forth in SEQ ID NO: 13). The Examiner alleges that as to these two mutants, it is not clear that a protein is even produced. The Examiner

further alleges that even if a protein were to be produced, it is well known in the art that protein chemistry is an unpredictable area of biotechnology. In addition, the Examiner alleges that as to antisense therapy, it is not clear as to how the mutations recited will affect antisense molecules and no teaching is provided to determine, in the mutants, which antisense molecules would function to treat cancer. Finally, the Examiner alleges that as to diagnosis of cancer, there is no teaching in the specification or in the art of record that any of the recited mutants are associated in any way with any type of cancer.

Applicant observes the specification discloses novel isolated and purified DNA molecules referred to as Sensitive to Apoptosis Genes ("SAG"), e.g., as set forth in SEQ ID 1 (mouse SAG) or SEQ ID 3 (human SAG), which encodes SAG proteins. See page 5, lines 9-21. Applicant observes that the present invention also provides DNA molecules substantially similar to those shown in SEQ ID 1 or SEQ ID 3, e.g., sequences recited in Claim 15. *Id.* The specification discloses that these novel purified and isolated DNA molecules can be used to direct expression of the SAG protein and for mutational analysis of SAG protein function. Applicant further observes that the specification teaches that SAG deletion mutants not only associate with cancer, e.g., colon and testicular cancer, but also are tumor-specific mutations. See, e.g., Example 21, starting at page 33. Moreover, Applicant observes that the specification discloses a method for inhibiting the growth of mammalian or non-mammalian tumor cells by introducing into the tumor cells an expression vector comprising a DNA that is antisense to a sequence substantially similar to the DNA molecule as set forth in SEQ ID 1 or SEQ ID 3 that is operatively linked to a DNA sequence that promotes the expression of the antisense DNA sequence. See, e.g., page 9, line 32 to page 10 line 9. Applicant observes that the specification

also discloses that antisense SAG expression inhibits tumor cell growth. See Example 17, starting at page 30.

In response, Applicant submits that the specification provides an adequate teaching regarding the generation of single and double SAG mutants in heme binding sites and zinc finger motif (e.g., in Example 8, on pages 21-23). Applicant also submits that the present application provides specific teachings that antisense SAG expression inhibits tumor cell growth (e.g., in Example 17, on pages 30-31); that SAG can be used as a target in cancer gene therapy by expressing antisense SAG (e.g., in Example 18, pages 31-32); that SAG mutations are cancer specific and can be used for diagnosing cancer (e.g., in Example 21, on pages 33-34). Therefore, the specification has provided sufficient description, guidance and working examples for those skilled in the art to make and use the claimed invention. For example, the specification demonstrates that expressing antisense SAG mRNA can inhibit cell growth by 60-75% (see, e.g., pages 30-31 in Example 17 and Figure 2). The specification also demonstrates that endogenous antisense SAG expression in tumor cell lines, e.g., from colon, prostate, kidney, lung and nasopharynx, blocks endogenous SAG synthesis, i.e., the normal SAG synthesis. See, e.g., Example 18 starting at page 31. The blocking of normal SAG synthesis renders tumor cells supersensitive to oxygen radicals, which leads to significant tumor shrinkage in treated tumors with or without drugs or radiation. *Id.* Applicant further submits that SAG mutants claimed in the present invention, e.g., SAG mutant-1 and SAG mutant-2, are substantially similar to SAG. See page 5, lines 9-21. It is well known in the art that an antisense RNA molecule substantially similar to the normal RNA transcripts will hybridize with the "sense" RNA made by the normal genes and thereby inhibit the synthesis of the corresponding protein, i.e., SAG protein in the present invention. Therefore, Applicant submits that although the specification does not provide

a working example, 35 U.S.C. § 112 does not require an applicant to provide all the detailed procedures for making and using the invention if the description of the invention itself is sufficient to permit one skilled in the art to make and use the invention.

Applicant acknowledges that additional experimentation, e.g., adjustment of certain parameters in different patients, may be required. However, such experimentation is routine to one skilled in the art and is not undue. Necessary experimentation is not determinative of the question of enablement; only *undue* experimentation is fatal under the provisions of 35 U.S.C. §112, first paragraph. *See, In re Wands*, 858 F.2d. 731, 736-737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

Accordingly, Applicant submits that the present application provides sufficient information for a person skilled in the art to make and use the present invention, in the absence of undue experimentation. Therefore, the rejection of 15-17, 25-26, 32 and 38, under 35 U.S.C. § 112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 25-26 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner alleges that Claims 25-26 are indefinite in the recitation of "A diagnostic assay" because it is not clear what the assay is diagnostic for.

In response, Applicant has amended Claims 25-26 to recite that the assay is diagnostic "for identifying cancer cells." Support for the amendment can be found throughout the specification, e.g., in Example 21, starting at 33. Accordingly, Claims 25-26, as amended, are clear and definite. Therefore, the rejection of Claims 25-26 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 2 and 9 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Boehringer Manheim Biochemicals, 1994 Catalog, page 93, Cat. Nos 1034 731

and 1006 924 ("Boehringer"). The Examiner alleges that Claims 2 and 9 are directed to a DNA sequence molecule that hybridizes to SEQ ID NOs: 1 and 3 under the claimed hybridization conditions. The Examiner indicates that Boehringer teaches a kit comprising random primers that encompass all possible 6-nucleotide sequences. Thus, the Examiner alleges that a subset of the Boehringer kit will hybridize to the claimed sequences under the claimed conditions.

In the first instance, Applicant observes that Claim 9 does not claim hybridization conditions but is directed to an isolated and purified DNA sequence that consists essentially of the DNA sequence as set forth in SEQ ID NO: 3. Applicant assumes that the Examiner may refer to Claims 2 and 8 in the rejection. Applicant further observes that Boehringer merely discloses a chemically synthesized mixture of hexa-nucleotides containing all possible 6-nucleotide sequences, which is used in random-primed method of radioactively-labeling DNA.

In response, Applicant submits that Claims 2 and 8 have been amended to recite "and wherein the polypeptide or protein encoded by said DNA molecule comprises at least one heme binding site or one zinc finger domain." The DNA sequence encoding either heme binding site or zinc finger domain has more than 6 nucleotides. Accordingly, Boehringer and Claims 2 and 9 (or 8) disclose different products. Applicant thus respectfully submits that Claims 2 and 9 (or 8) are not anticipated by Boehringer. Therefore, the rejection of Claims 2 and 9 under 35 U.S.C. § 102(b) is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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PIB/ZY:ab
Enclosure: Exhibit A

Exhibit A

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DATE: August 19, 2003

TO: Susan Unger
USPTO Examiner

NUMBER OF PAGES: 5

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RE: 09/509,779 Drawings
SAG: SENSITIVE TO APOPTOSIS GENE
Our Ref.: 5650-01-MG

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VIA FAX

Dear Examiner Unger,

As per our conversation this date, I am submitting the drawings that you requested.

Should you require further information or have any questions, please do not hesitate to contact me.

Very truly yours,

David R. Kurlandsky,
Patent Counsel

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